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Original Research

Clinical and prognostic value of pre-operative systemic inflammatory markers in clinical course and prognosis of ovarian cancer

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Summary

Objectives: Inflammation plays an important role in the pathogenesis of ovarian cancer. The prognostic value of systemic inflammatory markers is gaining importance in cancer patients. The aim of the present study is to evaluate the clinical and prognostic value of several inflammation markers to include neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and C-reactive protein (CRP), examined pre-operatively in epithelial ovarian cancer patients. *Design:* Retrospective clinical study. *Subjects:* A total of 97 patients with epithelial ovarian cancer who underwent primary staging surgery or debulking surgery were analyzed retrospectively. The influence of NLR, PLR values on overall survey (OS) was tested with Kaplan-Meier method and clinical-pathological parameters were tested with chi-square test. Proportional influence of clinical-pathological data on overall survival was tested with hazard ratio uni-variate and multi-variate analyses. *Results:* Median values of NLR, PLR and CRP were accepted as cut-off value. While elevated NLR (> 2.94) was associated with elevated CA-125 values ($p = 0.002$), excess amount of ascites ($p = 0.023$) and presence of residual tumor ($p = 0.036$); elevated PLR was associated with elevated CA-125 values ($p < 0.001$), excess amount of ascites ($p = 0.001$), presence of residual tumor ($p = 0.003$) and advanced stage ($p = 0.013$). Elevated CRP values were associated with only elevated CA-125 values ($p = 0.013$) and excess amount of ascites ($p = 0.046$). In uni-variate analysis, presence of post-operative residual tumor, > 500 cc ascites, NLR and PLR values were associated with OS; in multi-variate analysis, only stage ($p = 0.019$) and presence of post-operative residual tumor ($p = 0.016$) were found to be independent risk factors for OS. *Conclusion:* Novel prognostic biomarkers are urgently needed for better prediction of survival and definition of novel therapeutic targets.

Key words: Systemic inflammatory markers; Prognosis; Ovarian cancer.

Introduction

Ovarian cancer is the leading cause of gynecologic cancer-related deaths worldwide due to tumor heterogeneity and high metastasis potential [1]. A total of 14.270 ovarian cancer-related deaths were reported in the USA in 2014 [2, 3]. Almost half of the patients develop relapse within 16 months despite debulking surgery and adjuvant platinum-based chemotherapy, and 5-year survival is below 50% [4]. Survival rates vary widely even if the patients are at the same stage and received the same treatment. Traditional studies are focused on the tumor characteristics like histology and grade. Important parameters that show host response like tumor micro-environment and systemic inflammatory response (SIR) have gained importance only in the last decade [5].

Systemic inflammatory response is stimulated by proliferation of cancer cells, metastasis and angiogenesis [6]. Inflammation and immune response play an important role in initiation and progression of cancer and there is an increasing interest for the prognostic value of this response [7]. While neutrophil, platelet, C-reactive protein (CRP) and fibrinogen levels increase with the immune system response induced by SIR mediators, lymphocyte concentration decreases. Interleukin-6 (IL-6) which is an inflammatory cytokine was shown to lead to thrombocytosis through increasing hepatic thrombopoietin synthesis and para-neoplastic effect [8]. Inflammatory cytokines released by the tumor and ADP increase platelet count and aggregation by stimulating megakaryocytes. Vascular endothelial growth factor (VEGF) is quite important in tumor angiogenesis and the most important source is platelets. CRP is an acute phase reactant produced in hepatocytes against inflammation [9]. It increases angiogenesis in association

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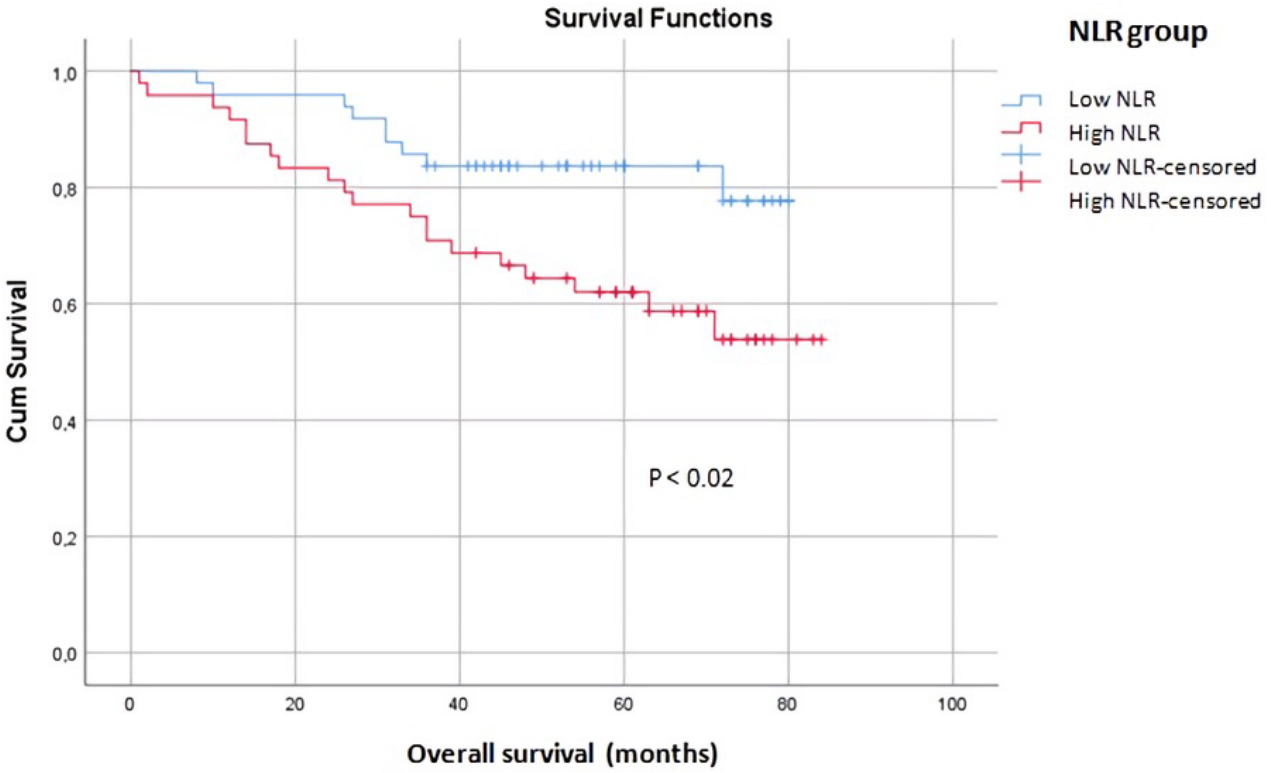

Figure 1. — Overall survival with low or high NLR.

with VEGF and IL elevation [10, 11]. Hofler showed the relationship between CRP elevation and poor survival and resistance to chemotherapy [12]. The SIR markers that are prognostic of oncologic outcomes including CRP, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and fibrinogen have been previously investigated in many different cancer types. In addition, they have been compared in an effort to identify the best prognostic marker [13-16]. In the present study, we investigated the clinical-pathological relationship between these inflammatory markers and ovarian cancer, their prognostic value and influence on overall survival.

Materials and Methods

Ethics committee approval was obtained from Çanakkale Onsekiz Mart University (date: 11.12.2019, number: 20-08).

Patients who were diagnosed with epithelial ovarian cancer between December 2012 and December 2019 in Istanbul Kanuni Sultan Suleyman Hospital and who received adjuvant platinum-based chemotherapy following primary debulking surgery were included. We excluded patients who received neo-adjuvant chemotherapy, who were diagnosed with non-epithelial ovarian tumor, who underwent surgery for recurrent disease, who had an active infection, secondary malignancy or history of auto-immune disease or who had no follow-up. Medical data and clinical and pathology results were obtained from hospital data management system.

All patients were followed every 3 months during the first 2 post-operative years and every 6 months thereafter in accordance with the treatment algorithm of the gynecologic oncology department of Istanbul Kanuni Sultan Süleyman Hospital. for the following information was obtained from the medical records: age, menopause status, stage (FIGO 2014), pre-operative laboratory data (CA 125, CRP, neutrophil count, lymphocyte count, platelet count), presence and amount of ascites, presence of post-operative residual tumor, date of the operation and the final status of the disease until December 2019. After surgical staging, stage I and II disease were categorized as early-stage, and stage III and IV disease as advanced-stage. Optimal surgery was defined as the presence of $\leq$ 1 cm residual tumor [17]. Neutrophil/lymphocyte ratio was defined as the ratio of absolute neutrophil count to lymphocyte count, PLR was defined as the ratio of platelet count to lymphocyte count. Preoperative blood tests were obtained from ante-cubital vein no mre than 1 week before surgery [18].

Overall survival was estimated as the duration between the date of the operation and death or the date of the last control.

Statistical Analysis

Medical data were obtained from the hospital data management system, clinical and pathology results were transferred to statistical software (SPSS 23). Patient character-

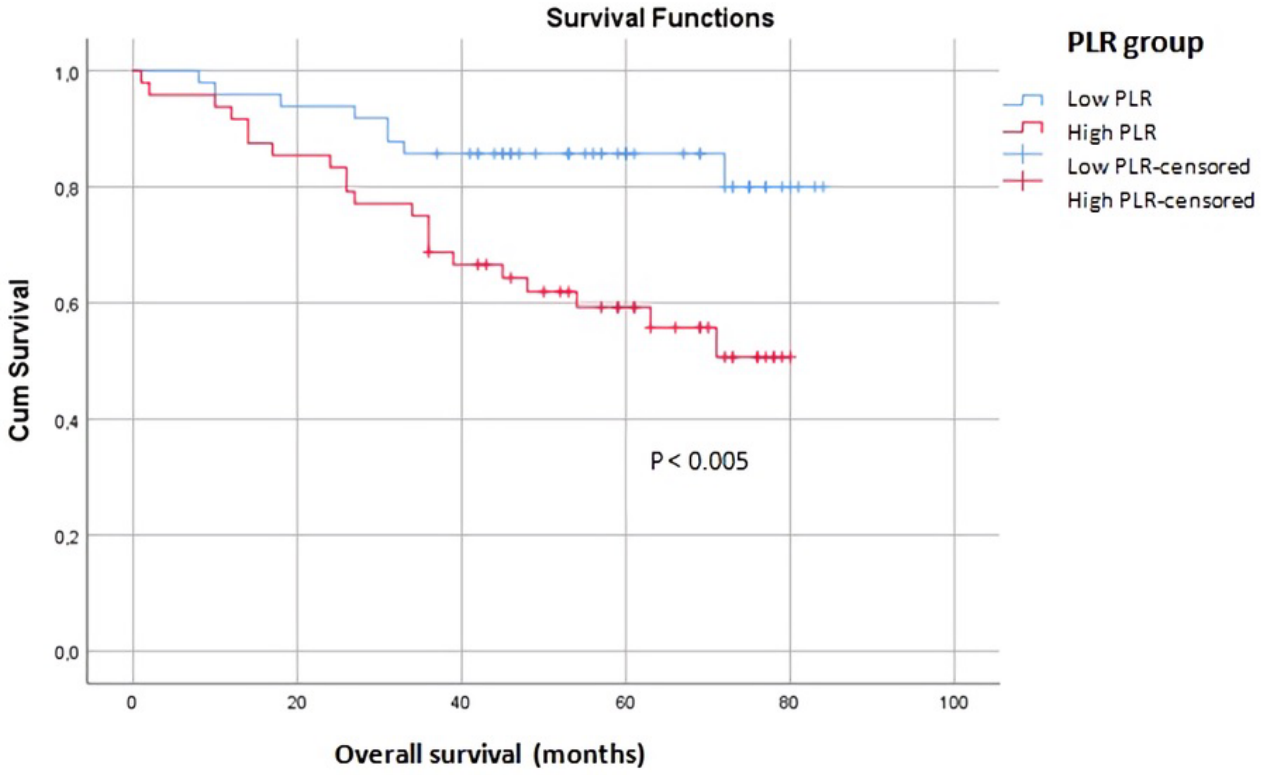

Figure 2. — Overall survival low or high PLR.

istics were expressed as percent and frequency, biochemical results were summarized as descriptive statistics (median, minimum and maximum). Normality distribution of biochemistry results was tested with Kolmogorov-Smirnov test. Data were detected not to be normally distributed ($p < 0.05$). So it was considered to be more appropriate to use arithmetic median rather than mean values. While arithmetic mean values are influenced from marginal data, the median is not [19, 20]. The values of NLR, PLR and CRP were assigned to one of two categories based on median values [18]. The values below the median were categorized as "low" and the values above the median were categorized as "high". The age of 50 years was used as the threshold value when making age categorization. CA 125 level of 500 IU/ml an above has been associated with advanced stage disease, suboptimal surgery prediction and disease recurrence in many studies [21, 22]. The relationship between the categorized/categorical data (NLR, PLR, CRP, phase, CA125, ascites, residual tumor) was tested using Chi-square independence test. As the values in the cells of the observed frequencies in the Chi-square test were not below 5, only "Pearson Chi-Square" values and the "*p* value" are taken into consideration. For overall survival, the effect of the variables on overall survival was measured with Cox regression univariate and multivariate hazard ratio, and the survival times were estimated using the Kaplan Meier Curve log-rank test [23].

Results

Mean age of the patients was 51 years (24-84). Of the patients, 64.9% (63/97) had advanced stage disease (stage 3/4) and optimal surgery was achieved in 72.2% (70/97). Median survival was 56 months (range 1-84 months). Median (inter-quartile range, IQR) neutrophil, platelet and lymphocyte counts were 5.7 (2.2-14) $\times$ 10^9/L, 329.10^3 (144-674.10^3), and 2 (0, 6-4) $\times$ 10^9/L, respectively. Median NLR, PLR and CRP values were accepted as cut-off values and NLR $>$ 2.94 was accepted as high, $\leq$ 2.94 was accepted as low; PLR $>$ 166.15 was accepted as high, $\leq$ 166.15 was accepted as low. Descriptive statistics of patient characteristics and biochemical variables are presented in Table 1.

The relationships between age, CA 125, NLR, PLR and CRP, and stage, ascites, residual tumor were tested with chi-square test. Pre-operative PLR elevation (PLR $>$ 166.5) was statistically significantly associated with advanced stage of cancer ($p = 0.013$), excess amount of ascites ($p = 0.001$), elevated CA 125 values ($p < 0.001$) and presence of post-operative residual tumor ($p = 0.003$). Elevated NLR ($>$ 2.94) was associated with excess amount of ascites ($p = 0.002$), elevated CA 125 values ($p = 0.002$) and presence of post-operative residual tumor ($p = 0.036$). Elevated CRP values were tested in only 19 patients and statistically significantly correlated with elevated CA 125 values ($p = 0.013$) and excess amount of ascites ($p = 0.046$) (Table 2).

Table 1. — *Patient characteristics.*

Variable		Number (N)		Percent (%)
Menopause	No	44		45.4
	Yes	53		54.6
Ascites	No	27		27.8
	$<$ 500 cc	25		25.8
	$\geq$ 500 cc	45		46.4
Optimal Surgery	Yes	70		72.2
	No	27		27.8
Survival	Deceased	29		29.9
	Alive	68		70.1
Stage (FIGO)	Early stage (I/II)	34		35.1
	Advanced stage (III/IV)	63		64.9
CA 125 (U/ml)	$<$ 500	65		67
	$>$ 501	32		33
Total		97		100
Variable		Median	Min	Max
Age (years)		51	24	84
CA 125		215	6	12198
Lymphocyte count		2	0.60	4
CRP		16	2.90	145
Neutrophil count		5.7	2.20	14
NLR		2.94	1.18	15.50
Platelet count		329000	144000	674000
PLR		166.15	72.42	562.50
Survival (months)		56	1	84

CA-125: cancer antigen 125 (U/ml), FIGO: International Federation of Gynecologists and Obstetricians, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, CRP: C-reactive protein.

In univariate analysis, while elevated NLR ($p = 0.025$), elevated PLR ($p = 0.008$), ascites amount of $\geq$ 500 cc ($p = 0.029$), presence of residual tumor ($p = 0.001$) and stage ($p = 0.004$) were significantly associated with OS; in multivariate analysis, only the presence of residual tumor and stage were satatistically significantly associated with OS (Table 3).

The association of PLR and NLR with OS was estimated with the Kaplan-Meier mehtod. Overall survival of the patients with NLR $>$ 2.94 was statistically significantly different from those with NLR $<$ 2.94 ($p \leq 0.02$) (Figure 1). Overall survival of the patients with PLR $>$ 166.15 was statistically significantly different from those whose PLR is $\leq$ 166.15 ($p < 0.005$) (Figure 2).

Figure 1 shows OS of patients with low and high NLR and Figure 2 shows OS for patients with high and low PLR.

Discussion

Survival widely varies among cancer patients even if they are at the same stage and same histologic type. Novel prognostic biomarkers are urgently needed for better prediction of survival and identification of novel therapeutic targets. The attention and interest paid to the relationship between systemic inflammatory markers and prognosis have gradually increased during recent decades [7].

Systemic inflammatory response (SIR) markers are the biochemical and hematological factors belonging to the host. The relationship between SIR and prognosis has been studied in different cancer types, however, very few studies have investigated the optimal prognostic markers and how these markers could impact treatment strategies [24].

Neutrophil/lymphocyte ratio is one of the markers of inflammatory response. It reflects the immunity status of the patient (pro-angiogenic and pro-inflammatory). Preclinical studies have shown that neutrophils stimulate tumor cell proliferation through β-TGF [25]. In addition, NLR increase is an indirect indicator of low lymphocyte-mediator response, which is associated with tumor progression and poor prognosis.

Elevated NLR has been shown to be associated with worse prognosis in many cancer types [26-29]. However, this relationship was not found in some studies [30-32]. In addition, data in ovarian cancer is quite limited. Williams stressed that elevated NLR not only indicated poor prognosis but also had an association with the clinical-pathological features of the disease like stage, grade and presence of ascites in 519 ovarian cancer patients [33]. Zheng-Feng found that elevated NLR was associated with advanced stage, CA 125 elevation and excess amount of ascites and reported that it could predict the feasibility of cyto-reduction [18].

Platelet/lymphocyte ratio is another indicator of systemic inflammatory response. Inflammatory cytokines and ADP released by the tumor increase platelet count and aggregation by stimulating megakaryocytes. Vascular endothelial growth factor (VEGF) is quite important in tumor angiogenesis and the most important source is platelets. Thrombocytosis reflects a systemic inflammation and also contributes to tumor cell invasion and metastasis [34, 35]. Asher reported PLR as an independent prognostic factor in 235 ovarian cancer patients [36]. Thrombocytosis was also shown to predict poor survival [37]. Stone suppressed tumor growth by reducing platelet count with anti-IL6 treatment [8].

Clinical studies have revealed that NLR and PLR are prognostic markers in many different cancer types [38-40]. They were emphasized as valuable predictors of in ovarian cancer [41].

Wei-Wei Zhang *et al*. found PLR superior to the other markers for prediction of ovarian cancer survival [24]. Raungkaewmanee also stated that PLR is a better prognostic indicator than NLR and thrombocytosis in his study that included 166 patients, but in multivariate analysis he did not find PLR to be a significant predictor of OS [42].

Ceran *et al*. concluded that an elevated PLR was associated with a 2.53 times increase in mortality. However, PLR and NLR were similarly weak and not associated with OS. Their median PLR and NLR values are very close to the values in our study, but they considered the results of the

Table 2. — *Clinical paremeters and NLR, PLR, CRP.*

Parameters	NLR		*p*-value	PLR		*p*-value	CRP		*p*-value
	Low	High		Low	High		Low	High	
Age									
< 50 (48)	22 (45.8)	26 (54.2)	0.361	23 (47.9)	25 (52.1)	0.610	7 (58.3)	5 (41.7)	0.960
≥ 51 (49)	27 (55.1)	22 (44.9)		26 (53.1)	23 (46.9)		4 (57.1)	3 (42.9)	
FIGO (Stage)									
Stage I-II (34)	20 (58.8)	14 (41.2)	0.229	23 (67.6)	11 (32.4)	0.013*	6 (66.7)	3 (33.3)	0.463
Stage III-IV (63)	29 (46)	34 (54)		26 (41.3)	37 (58.7)		5 (50)	5 (50)	
CA 125 level									
< 500 (65)	40 (61.5)	25 (38.5)	0.002**	41 (63.1)	24 (36.9)	0.001**	10 (76.9)	3 (23.1)	0.013*
≥ 500 (32)	9 (28.1)	23 (71.9)		8 (25)	24 (75)		1 (16.7)	8 (83.3)	
Ascites									
No (27)	17 (63)	10 (37)		21 (77.8)	6 (22.2)		4 (80)	1 (20)	
< 500 cc (25)	16 (64)	9 (36)	0.023*	14 (56)	11 (44)	0.001**	5 (83.3)	1 (16.7)	0.046*
≥ 500 cc (45)	16 (35.6)	29 (64.4)		14 (31.1)	31 (68.9)		2 (25)	6 (75)	
Residual tumor									
≤ 1 cm (70)	40 (57.1)	30 (42.9)	0.036*	42 (60)	28 (40)	0.003**	10 (66.7)	5 (33.3)	0.134
> 1 cm (27)	9 (33.3)	18 (66.7)		7 (25.9)	20 (74.1)		1 (25)	3 (75)	

CA-125: cancer antigen 125 (U/ml), FIGO: International Federation of Gynecology and Obstetrics.
NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, CRP: C-reactive protein.
*Chi-Square Test *p < 0.05 is considered to be statistically significant, **p < 0.01 is considered to be statistically significant.*

Table 3. — *Univariate and multivariate analysis results of overall survival.*

Variables	Univariate			Multivariate		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age (≤ 50, > 50)	1.017	0.988-1.046	0.249			
CA 125 (≤ 500, > 500)	1.192	0.454-3.128	0.721			
NLR (≤ 2.94, > 2.94)	2.465	1.121-5.416	0.025*			
PLR (≤ 166.15, > 166.15)	3.036	1.344-6.859	0.008**			
CRP (≤ 16, > 16)	0.992	0.965-1.021	0.592			
No ascites			0.042*			
Ascites < 500 cc	1.45	0.389-5.399	0.580			
Ascites ≥ 500 cc	3.297	1.126-9.65	0.029*			
Post-operative residual tumor (cm) (≤ 1 cm, > 1 cm)	5.129	2.417-10.882	0.001**	2.589	1.191-5.626	0.016*
Stage (FIGO) (I/II, III/IV)	19.495	2.65-143.396	0.004**	11.784	1.507-92.151	0.019*

HR: hazard ratio, CI: confidence interval.
CA-125: cancer antigen 125 (U/ml), FIGO: International Federation of Gynecology and Obstetrics.
NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, CRP: C-reactive protein.
**p < 0.05 is considered to be statistically significant, **p < 0.01 is considered to be statistically significant.*

ROC analysis when determining the cut off value [43].

In our study, NLR > 2.94 and PLR > 166.15 were found to be statistically significantly associated with OS.

CRP/albumin ratio is important for reflecting nutritional status, as well as the inflammatory response of cancer patients. Post-operative residual tumor and stage are known to be the most reliable prognostic indicators for survival in ovarian cancer [44]. Liu *et al.* reported a hazard ratio of 2.33 and 1.57 for residual tumor and stage, respectively. The hazard ratio was 1.33 for CRP/albumin in multivariate analysis that included residual tumor and stage. Liu *et al.* emphasized that this parameter is a novel independent poor prognosis indicator that provides more valuable information that indices only of of inflanmmation rather than inflammation and nutritional status [9]. Unfortunately, this parameter could not be evaluated in our study as preoperative albumin values were available in only few patients. C-reactive protein is not routinely tested, and it is not widely used in clinical practice [45].

Limitations of the present study include its retrospective design. NLR and PLR cutoff values could be calculated with ROC analysis or using median value, as in our study.

The diversity of cutoff values among published studies reduces their clinical use. It would be better to obtain the baseline values of the patients and make comparisons.

Authors' contributions

S.H.O. and A.Z. conceived and designed the study; S.H.O., A.Z. and T.I.U. performed the study; T.C. and Y.I.T analyzed the data; S.A. and A.O. contributed materials and evaluation; S.H.O and A.Z. wrote the paper.

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Conflict of Interest

The authors declare no conflict of interest.

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